PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61K 9/22	A1	(11) International Publication Number: WO 87/ 02240
		(43) International Publication Date: 23 April 1987 (23.04.87)

(21) International Application Number: PCT/SE86/00400

(22) International Filing Date: 10 September 1986 (10.09.86)

(31) Priority Application Number: 8504720-7

(32) Priority Date: 11 October 1985 (11.10.85)

(33) Priority Country: SE

(71) Applicant: AKTIEBOLAGET HÄSSLE [SE/SE]; S-431 83 Mölndal (SE).

(72) Inventors: DAHLINDER, Lars-Erik, David ; Rågkornsgatan 60, S-431 40 Mölndal (SE). JOHANSSON, Mats, Ove ; Tångenvägen 13, S-417 43 Göteborg (SE). SANDBERG, John, Anders ; Hökegårdsgatan 57, S-431 38 Mölndal (SE). SJÖGREN, John, Albert ; Kullbäckstorpsvägen 40, S-435 00 Mölnlycke (SE).

(74) Agents: MIKSCHE, Gerhard et al.; AB Astra, Patent and Trademark Department, S-151 85 Södertälje (SE).

(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SD, SE (European patent), SU.

Published
With international search report.

(54) Title: NEW DRUG PREPARATION WITH CONTROLLED RELEASE OF THE ACTIVE COMPOUND, A METHOD FOR THE MANUFACTURE THEREOF AND THE USE OF THE NEW PREPARATION

(57) Abstract

Controlled release preparation containing a number of insoluble beads applied with one or more pharmaceutically active compounds, a method for the production thereof and the use in a treatment where a controlled release of a pharmaceutically active compound is needed.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**FR**	France	**ML**	Mali
AU	Australia	**GA**	Gabon	**MR**	Mauritania
BB	Barbados	**GB**	United Kingdom	**MW**	Malawi
BE	Belgium	**HU**	Hungary	**NL**	Netherlands
BG	Bulgaria	**IT**	Italy	**NO**	Norway
BJ	Benin	**JP**	Japan	**RO**	Romania
BR	Brazil	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SN**	Senegal
CH	Switzerland	**LI**	Liechtenstein	**SU**	Soviet Union
CM	Cameroon	**LK**	Sri Lanka	**TD**	Chad
DE	Germany, Federal Republic of	**LU**	Luxembourg	**TG**	Togo
DK	Denmark	**MC**	Monaco	**US**	United States of America
FI	Finland	**MG**	Madagascar		

New drug preparation with controlled release of the active compound, a method for the manufacture thereof and the use of the new preparation

Field of the Invention

The present invention is related to new pharmaceutical preparations with controlled release of a pharmaceutically active compound, to a method for the manufacture of such preparations and to a method of obtaining controlled release of a pharmaceutically active compound.

Background of the Invention

In the medical treatment of various diseases, e.g. in the cardiovascular, gastrointestinal and chemotherapeutic field, it is an advantage to have a constant concentration of the administered drug in the blood. Thus a controlled release of the drug from the pharmaceutical preparation is wanted.

It is important that the controlled release preparation delivers the amount of drug needed to maintain an adequate and even effect during the entire therapeutic dosage interval. This usually means that the drug should be delivered at a constant rate to give an even concentration of the administered drug in the blood which is of specific importance for drugs having a small therapeutic index, i.e. a small difference between effective and toxic concentration. A delayed and constant release of the drug will also be of importance for locally irritating drugs having a potential risk of causing gastrointestinal disturbances when present in large local concentrations or for drugs having a short elimination half-life. In the latter case less frequent administration and thus better patient compliance (cf. Hayes R.B. et al. Clin. Pharm. Therap. (1977), 22, p. 125-130) may be obtained with controlled release preparations compared with conventional dosage forms.

A drug can be delivered in a controlled way via any route of administration but the preparations should preferably have some features in common, e.g. give a controlled and reproducible release of drug and contribute to a reproducible absorption, have no toxic or irritating constituents and be suitable also for high dosage drugs.

Examples of drug delivery systems for oral use with a controlled release of the drug are e.g. sustained release tablets of the insoluble matrix type, such as Durules®, and the osmotically active tablet, OROS®. The OROS® system is described in U.S. Patent 4 036 227 and in a supplement to British Journal of Clinical Pharmacology (1985), 19, 695-765 by Theeuwes F. et al. It consists of a tablet core of the drug substance as the major constituent which is surrounded with a semipermeable polymeric membrane through which a small opening is drilled. DE-A-2030501 describes a preparation of the matrix type which contains amorphous silicon dioxide. The active compound is released by diffusion through the matrix. The examples above are single-unit systems with all drug substance concentrated in one unit while the present invention is of the multiple-unit principle.

From GB-A-1542414 a composition is known containing an organic support material to which an active compound is physically or chemically bound and a glass material in contact with said support material. The glass contains soluble metal ions. The release of drug is governed by the dissolution of metal ions from the glass material due to an ion exchange process. Obviously, the glass is not an insoluble inert compound of the composition.

Several advantages with depot preparations comprising a large number of small units have been described in the literature. It is, for example, possible to obtain a reproducible emptying of the units from the stomach into the small intestine when the particles are less than 1-2 mm (cf. Bogentoft C. et al: Influence of food on the absorption of acetylsalicylic acid from enteric coated dosage forms. Europ. J. Clin. Pharmacol. (1978), 14, 351-355). Dispersion over a large area in the gastrointestinal canal can give a more reproducible total time for the passage, which is of advantage for the absorption process (cf. Edgar B. et al: Comparison of two enteric-coated acetylsalicylic acid preparations by monotoring steady-state levels of salicylic acid and its metabolites in plasma and urine. Biopharmaceutics & Drug Disposition, (1984), 5, 251-260). In addition a multiple unit preparation is preferable to one single drug unit as the dose is spread out in the intestine. The risk of local irritation and accumulation of several

doses due to constriction in the alimentary canal are also considered to be lower, (cf. McMahan F.G. et al: Upper gastrointestinal lesions after potassium chloride supplements: A controlled clinical trial The Lancet, Nov 13, 1059-1061).

A further advantage with a multiple unit preparation is that it may be divided into smaller portions all having the same absorption properties. This makes it possible to obtain a greater flexibility in selecting the size of the dose.

Outline of the Invention

The present invention is related to a new type of preparation giving a controlled release of one or more pharmaceutically active compounds.

The preparation consists of a large number of small insoluble particles, cores, which are covered by a pharmaceutically active compound. The cores have a size of 0.1-2 mm, preferably 0.1-0.5 mm, and consist of insoluble inert material. Insoluble means that the material is not soluble in water, physiological fluids or in common liquids used for intravenous infusion. Examples of insoluble inert material are silicon dioxide, glass, or plastic resin particles. Suitable types of plastic materials are pharmaceutically acceptable plastics, such as polypropylene or polyethylene, preferably polypropylene. The core material should have a standardized size and shape, preferably spherical with an even surface. Preferably, the core material should have a sufficiently high density which makes it suitable for a fluidized-bed process. Furthermore, it is important that the core material has a high degree of purity, that is, is free from soluble contaminating compounds.

The pharmaceutically active compound is applied on the core material preferably by spraying from a solution. The active compound thereby forms a compact layer on the insoluble core. Pharmaceutically active compounds used are such having cardiovascular, gastrointestinal or chemotherapeutic effect, especially adreneric beta-blocking agents and antibiotics. Examples of suitable pharmaceutically active compounds which can be applied on the core material are salts of alprenolol,

metoprolol, quinidine, magnesium, and ampicillin. The resulting particles or beads have a size of 0.2-3.0 mm, preferably 0.3-1.0 mm. It is however possible to form controlled release preparations according to the method above for most drugs for which such preparations are wanted, provided they can be dissolved in a solvent that can be dried off during processing.

The beads according to the invention are compact, which means that the porosity is less than 15 per cent.

The beads are coated with a polymeric membrane modifying and controlling the drug release. The polymeric membrane can release the drug according to various release profiles, e.g. pH dependent, enteric coating, pH independent, with or without lag time. The most important use is pH independent controlled release in the range of pH 1-8. Examples of suitable polymeric materials are ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl phthalate (e.g. HP 55), cellulose acetate phthalate, Eudragit® RL, Eudragit® RS. Ethyl cellulose can be used alone or in a combination with e.g. a water soluble polymer such as hydroxypropylmethyl cellulose to adjust the permeability of the coating layer.

Ethyl cellulose is available in grades having different viscosities. In the examples given below, ethyl cellulose qualities with a viscosity of 10, 50 or 100 cps are used, but also other types of ethyl cellulose are suitable.

Eudragit® is the trade name for a number of film coating substances on an acrylic resin basis produced by Röhm Pharma. E.g. Eudragit RL and RS are copolymers synthetized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The molar ratio of these ammonium groups to the remaining neutral (meth)acrylic acid esters is 1:20 for Eudragit® RL and 1:40 for Eudragit® RS resulting in different permeability characteristics. Other variants of Eudragit that can be used are Eudragit L, Eudragit S and Eudragit E.

Pigments and/or plasticizers may be added to the polymeric solution in order to improve the technical properties of the membrane or modify the release characteristics. Examples of plasticizers that may be used are citrate esters, acetylated monoglycerides, and glycerinetriacetate.

The new preparation has several advantages, e.g. the particles contain a high percentage of active ingredient and are not contaminated by soluble inert compounds, which is the case, when cores of e.g. lactose or sugar are covered by a therapeutically active compound. This is especially important when the preparation is used for parenteral administration.

By using small dense particles of e.g. silicon dioxide as the core material, it is possible to obtain highly concentrated beads (granules) of the active compound which is an advantage for high dosage preparations, e.g. magnesium chloride.

An advantage with the new preparation is that in general less polymeric material is needed to obtain a delayed drug release when the insoluble cores applied with an active compound are coated compared to when preparations having a soluble core material are coated (cf. Figure 1). The preparation according to the invention can be administered by various routes, e.g. orally or parenterally. An example of intravenous administration is via the drug-administration-device described in EP-B1-59694.

When using the coated beads of active compound according to this invention for oral application, it is possible to formulate the preparation as granules filled into hard gelatine capsules, filled into sachets or formed into tablets and still obtain the desired plasma concentration profile and duration of the effect after administration.

When the small beads are tabletted they are mixed with additives containing e.g. microcrystalline cellulose, such as Avicel®, which improves the tabletting properties and facilitates the disintegration of the tablet to liberate the individual beads.

The invention makes it possible to obtain a decreased dosing frequency and still have an almost constant concentration of the drug in the plasma during the whole period until the next dose is administered. A single dose a day is often sufficient with the new preparation.

A process for the manufacture of a controlled release preparation represents a further aspect of the invention. The pharmaceutically active compound is dissolved in a suitable solvent e.g. methylene chloride, ethanol, isopropylic alcohol or water and sprayed onto the insoluble core material in a coating pan or preferably in a fluidized bed and the solvent is dried off. The beads obtained are then coated with a polymeric layer described above. The polymeric mixture is dissolved in a solvent such as ethanol, isopropyl alcohol and/or methylene chloride. The spraying can be carried out in a coating pan, but is preferably carried out in a fluidized bed. Ethyl cellulose can also be applied from an aqueous dispersion (latex).

The preparation according to the invention is particularly advantageous when a controlled and constant release of a therapeutically active compound is wanted. A method for the controlled release of therapeutically active compounds represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Example 1

Cores

Metoprolol fumarate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
SiO_2 (0.15-0.25 mm)	375 g

Polymeric layer

Ethyl cellulose 10 cps	265.6 g
Hydroxypropylmethyl cellulose	58.4 g
Acetyltributylcitrate	36.0 g
Methylene chloride	6141 g
Isopropylic alcohol	1544 g

In a fluidized bed granulator metoprolol fumarate was sprayed onto the cores of silicon dioxide from a solution of ethanol 95%. 400 g of the beads so formed (fraction 0.4-0.63 mm) were covered with the polymeric solution containing ethyl cellulose 10 cps, hydroxypropylmethyl cellulose and acetyltributylcitrate by spraying a solution of the mentioned substances in methylene chloride and isopropylic alcohol. The coated beads were then filled into hard gelatine capsules.

Examples 2-3 and Reference 1

Cores

	2	3	Reference 1
Metoprolol succinate	1440 g	1440 g	1440 g
Methylene chloride	9618 g	9618 g	9618 g
Ethanol 95%	3888 g	3888 g	3888 g
SiO_2 (0.15-0.25 mm)	375 g		
Glass (0.2 mm)		375 g	
NaCl (0.15-0.25 mm)			375 g

Polymeric layer

400 g of the granules (fraction 0.4-0.5 mm) above were coated with a composition comprising

Ethyl cellulose 10 cps	52.3 g
Acetyltributylcitrate	8.6 g
Methylene chloride	1111 g
Isopropylic alcohol	218 g

Metoprolol succinate was sprayed onto the cores of silicon dioxide, glass and sodium chloride, respectively, from a solution of ethanol 95% and methylene chloride. The beads so formed were coated with the polymeric solution containing ethyl cellulose 10 cps and acetyltributylcitrate dissolved in methylene chloride and isopropylic alcohol by spraying. Figure 1 illustrates the cumulative release of metoprolol succinate during 20 hours. As can be seen from the figure a controlled and almost constant release of the active compound was obtained, when the active compound was applied on silicon dioxide or glass, whereas a core of soluble sodium chloride resulted in a considerably higher initial release rate, which also is illustrated in Figure 2 (Reference 2 below) where soluble potassium chloride was used as core material.

Reference 2

Cores

Metoprolol succinate	2000 g
KCl (0.1-0.2 mm)	400 g
Methylene chloride	13360 g
Ethanol 95%	7900 g

400 g of the granules according to Reference 2 were coated with a composition comprising

Polymeric layer

Ethyl cellulose 10 cps	135.3 g
Eudragit® RS	27.4 g
Acetyltributylcitrate	27.4 g
Methylene chloride	4469 g
Isopropylic alcohol	661 g

The granules were formulated as described in the previous examples.

Examples 4-6

Cores

	Example 4	5	6
Metoprolol succinate	1440 g	1440 g	1440 g
Methylene chloride	9618 g	9618 g	9618 g
Ethanol 95%	3888 g	3888 g	3888 g
SiO_2 (0.15-0.2 mm)	375 g		
SiO_2 (0.25-0.3 mm)		375 g	
SiO_2 (0.4-0.5 mm)			375 g

400 g of the granules according to Examples 4-6 were coated with a composition comprising

Polymeric layer

	granulate according to Example 4	5	6
Ethyl cellulose 10 cps	187.2 g	144.0 g	92.2 g
Hydroxypropylmethyl cellulose	46.8 g	36.0 g	23.0 g
Acetyltributylcitrate	26.0 g	20.0 g	12.8 g
Methylene chloride	4428 g	3408 g	2168 g
Isopropylic alcohol	1114 g	858 g	546 g

The preparations were formulated as described above. In the enclosed Table 1 the release of metoprolol succinate during 20 hours is given. All preparations gave a controlled release of drug during a long period of time.

Example 7

Cores

Magnesium chloride, hexahydrate	1100 g
Ethanol 99.5%	6200 g
Silicon dioxide (0.15-0.30 mm)	400 g

Polymeric layer

Ethyl cellulose 50 cps	533 g
Methylene chloride	14107 g
Isopropylic alcohol	5481 g

Magnesium chloride ($MgCl_2$) was sprayed onto the cores of silicon dioxide from a solution of ethanol 99.5%. 400 g of the beads so formed were coated with ethyl cellulose 50 cps from a solution of methylene chloride and isopropylic alcohol to give granules containing 347 mg/g magnesium chloride ($MgCl_2$). The in vitro release of drug was 38% after 1 hour, 58% after 2 hours and 82% after 6 hours.

Example 8

Cores

Ampicillin - Na	600 g
Ethanol 95%	894 g
Water purified	1020 g
Glass (0.5 mm)	500 g

Polymeric layer

Ethyl cellulose 100 cps	15 g
Methylene chloride	600 g
Isopropylic alcohol	150 g

Ampicillin-Na was sprayed onto the cores of glass from the ethanol/water solution. 500 g of the ampicillin-Na beads were then coated with a polymeric solution of ethyl cellulose 100 cps in methylene chloride/isopropylic alcohol. After 40 minutes in vitro dissolution 50% of the drug content was released from the beads.

Example 9

Cores

Metoprolol succinate	1440 g
Methylene chloride	9618 g
Ethanol 95%	3888 g
SiO_2 (0.15-0.25 mm)	375 g

Polymeric layer

Ethyl cellulose N-10	166.2 g
Hydroxypropylmethyl cellulose	39.0 g
Acetyltributylcitrate	22.8 g
Methylene chloride	3889 g
Isopropylic alcohol	978 g

Tablet additives

Microcrystalline cellulose	429.3 g
Corn starch	67.1 g
Lactose powder	40.3 g
Polyvidone	55.5 g
Water purified	314.7 g
Magnesium stearate	1.2 g

Tablet coating (12.500 tablets)

Hydroxypropylmethyl cellulose 6 cps	159.6 g
Polyethylene glycol 6000	39.9 g
Colour Titanium Dioxide	39.9 g
Water purified	1356 g
Paraffin	1.6 g

Metoprolol succinate was sprayed onto the cores of silicon dioxide according to the process described in the previous examples. 400 g of the so obtained beads (fraction 0.4-0.63 mm) were coated with the poly-

meric solution described above. The coated beads of metoprolol succinate were mixed with the additives in equal portions and after addition of Mg-stearate 0.1%, the dry mixture was compressed to tablets. Finally, the tablets were coated in a coating pan with the polymeric solution described above.

The very small particles, 0.15-0.25 mm, of dense SiO_2 used as the core material, contribute to a high content of drug in the small beads formed (0.4-0.63 mm) and thus to a reduced size of the final preparation.

Table 1 summarizes the drug release data for the compositions according to examples 1-6 and 9 and Reference examples 1 and 2.

Biopharmaceutical studies

An oral application of the present invention (Example 9) is illustrated in Figure 3. The multiple-unit system was applied on metoprolol succinate in order to find a preparation for dosage once daily with an even plasma concentration profile over 24 hours.

A single dose of 190 mg metoprolol succinate (equivalent to 200 mg metoprolol tartrate) in a controlled release preparation according to the present invention was administered to 10 healthy male subjects. The plasma concentrations of metoprolol were compared with the plasma concentrations after a single dose of a sustained release tablet (Durules®) based on the insoluble matrix principle containing 200 mg of metoprolol tartrate. As can be seen the preparation according to the invention gave an almost constant plasma concentration profile of metoprolol, whereas the matrix tablet gave an unwanted high peak in the plasma concentration during the first hours after the administration.

The best mode of carrying out the invention is at present considered to be Example 9.

Table 1. Cumulative in vitro release of metoprolol in a phosphate buffer pH 6.8
Method: USP apparatus No II, rotating paddle at 100 rpm

Example No.	Fig. No.	Core material	Conc. metoprolol in the beads mg/g	Per cent release over time (h)											
				1	2	3	4	6	8	10	12	14	16	18	20
1		SiO_2	434	1	2	5	11	25	39	52	62	69	74	78	81
2	1	SiO_2	703	9	15	22	27	38	47	56	64	71	78	84	88
3	1	glass	688	12	20	28	34	45	55	63	71	77	84	89	92
Ref. 1	1	NaCl	686	5	32	51	65	81	89	93	96	98	99	100	100
Ref. 2	2	KCl	619	8	23	32	40	53	63	73	79	84	87	90	92
4		SiO_2	513	1	2	3	8	21	34	48	61	72	80	84	88
5		SiO_2	565	1	2	4	8	19	29	40	51	62	71	78	83
6		SiO_2	620	4	8	12	17	28	37	46	54	62	68	74	79
9	3	SiO_2	533	7	13	18	23	33	43	52	61	69	76	82	86

CLAIMS

1. Controlled release beads coated with a membrane controlling the drug release characterized in that they contain one or more pharmaceutically active compounds applied on a compact insoluble core material, whereby the active compound forms a compact layer on the insoluble core and this compact layer is further covered with a release controlling polymeric membrane.

2. Beads according to claim 1 characterized in that the size of the particles of the core material is 0.1-2 mm and the size of the core covered with pharmaceutically active compound is 0.2-3.0 mm.

3. Beads according to claim 2 characterized in that the core material has a size of 0.1-0.5 mm and that said core material covered with pharmaceutically active compound has a size of 0.3-1.0 mm.

4. Beads according to claim 1 characterized in that the core material is silicon dioxide.

5. Beads according to claim 1 characterized in that the core material is small particles of glass.

6. Beads according to claim 1 characterized in that they contain a pharmaceutically active compound for which a non instant drug release is wanted.

7. Beads according to claim 1 characterized in that the pharmaceutically active compound is to be administered orally or parenterally.

8. Beads according to claim 1 characterized in that the pharmaceutically active compound is used in the cardiovascular, gastrointestinal or chemotherapeutic field.

9. Beads according to claim 1 c h a r a c t e r i z e d i n t h a t the pharmaceutically active compound is a salt of an adrenergic beta-blocking agent.

10. Beads according to claim 1 c h a r a c t e r i z e d i n t h a t the pharmaceutically active compound is an antibiotic.

11. Process for the preparation of beads for the production of controlled release products c h a r a c t e r i z e d i n t h a t a pharmaceutically active compound dissolved in a solvent is applied onto insoluble core material with a size of 0.1-2 mm, the solvent is dried off and beads covered with a compact layer of active compound and having a size of 0.2-3.0 mm are obtained, whereafter the obtained beads are further covered with a release controlling polymeric membrane.

12. Method for obtaining controlled release of therapeutically active compound c h a r a c t e r i z e d i n t h a t a composition according to claim 1 is administered to a host in the need of a controlled release of said therapeutically active compound.

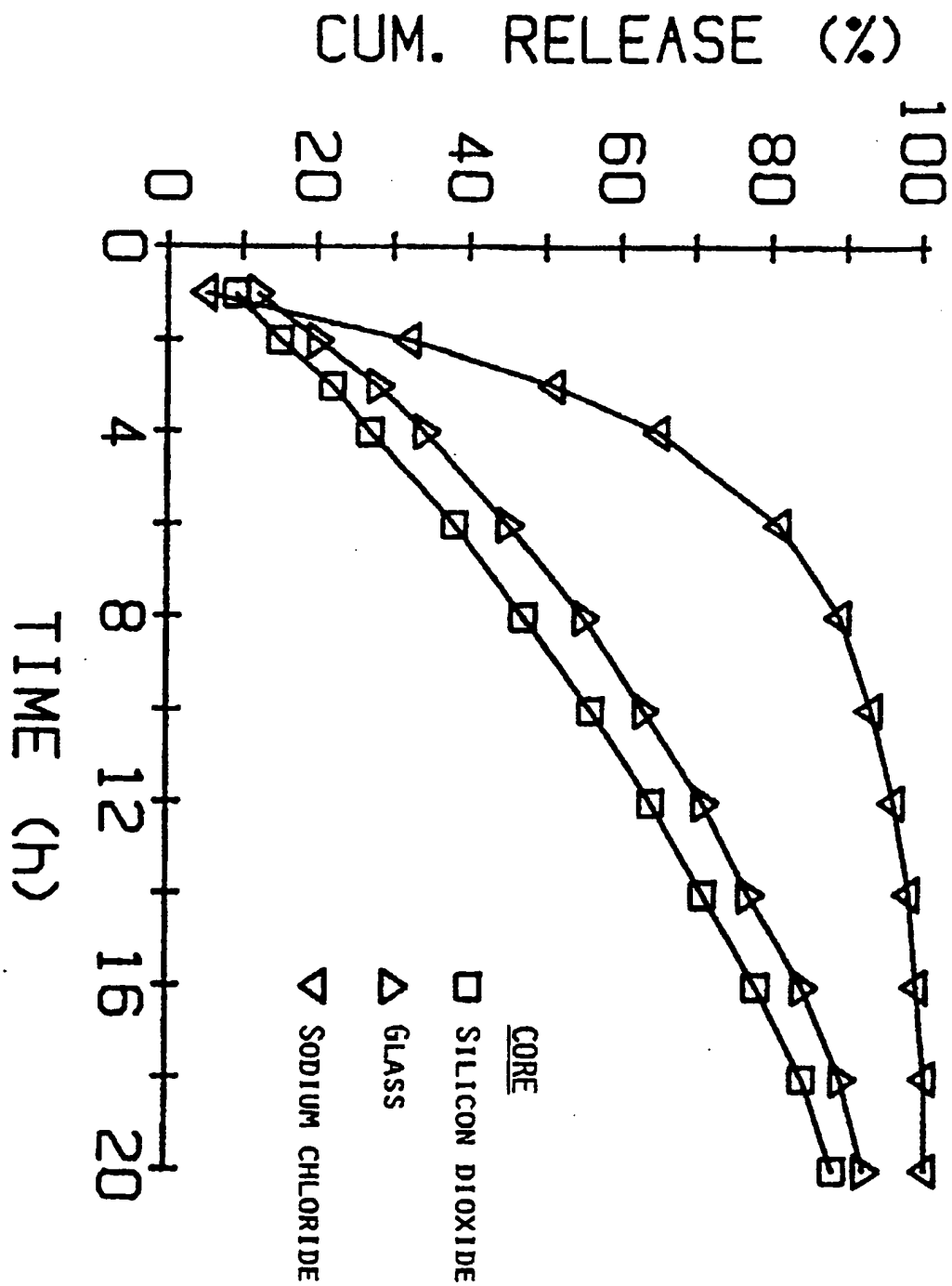

CUM. RELEASE (%)
0
20
40
60
80
100
TIME (h)
0
4
8
12
16
20
CORE
SILICON DIOXIDE
GLASS
SODIUM CHLORIDE

FIGURE 1

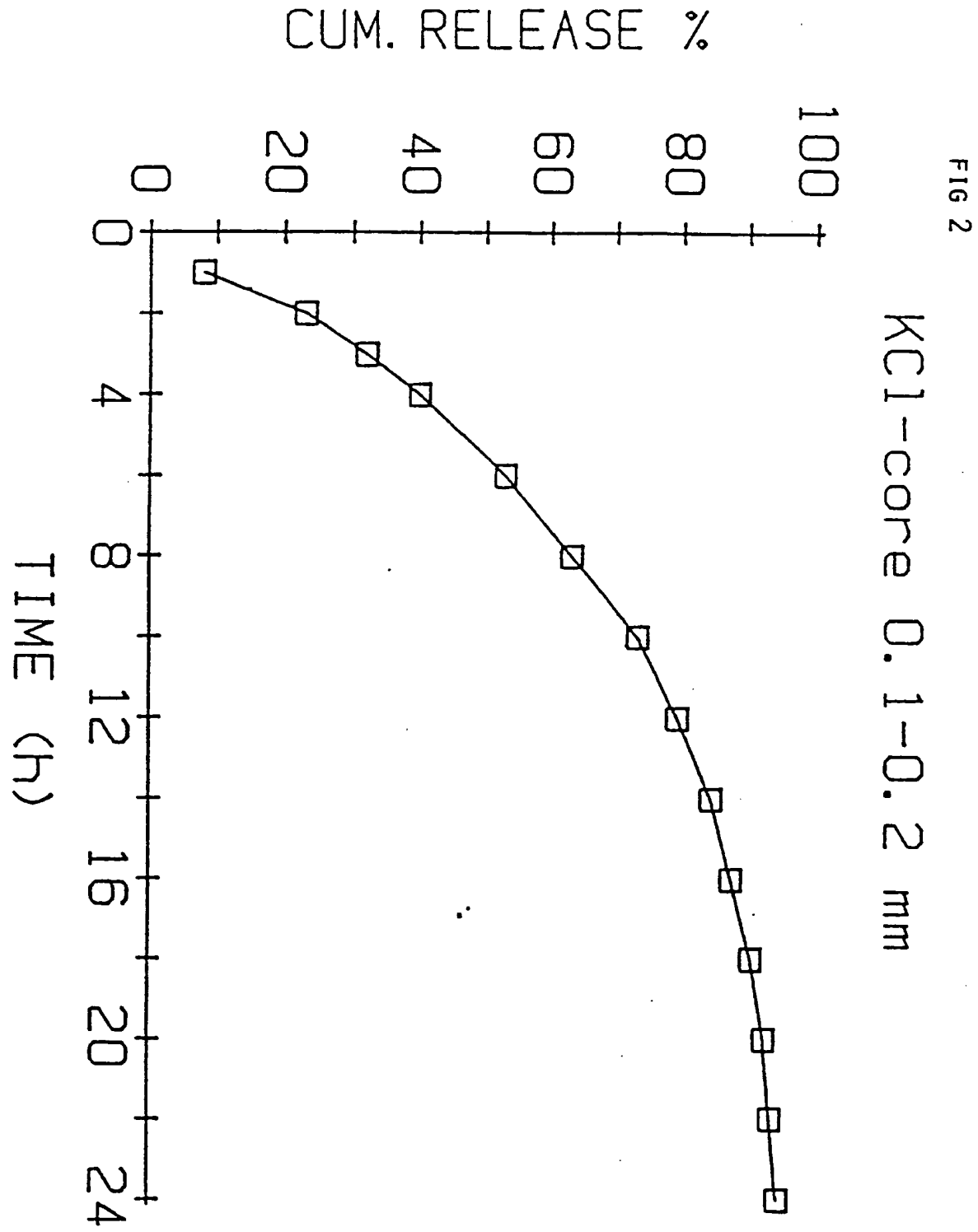
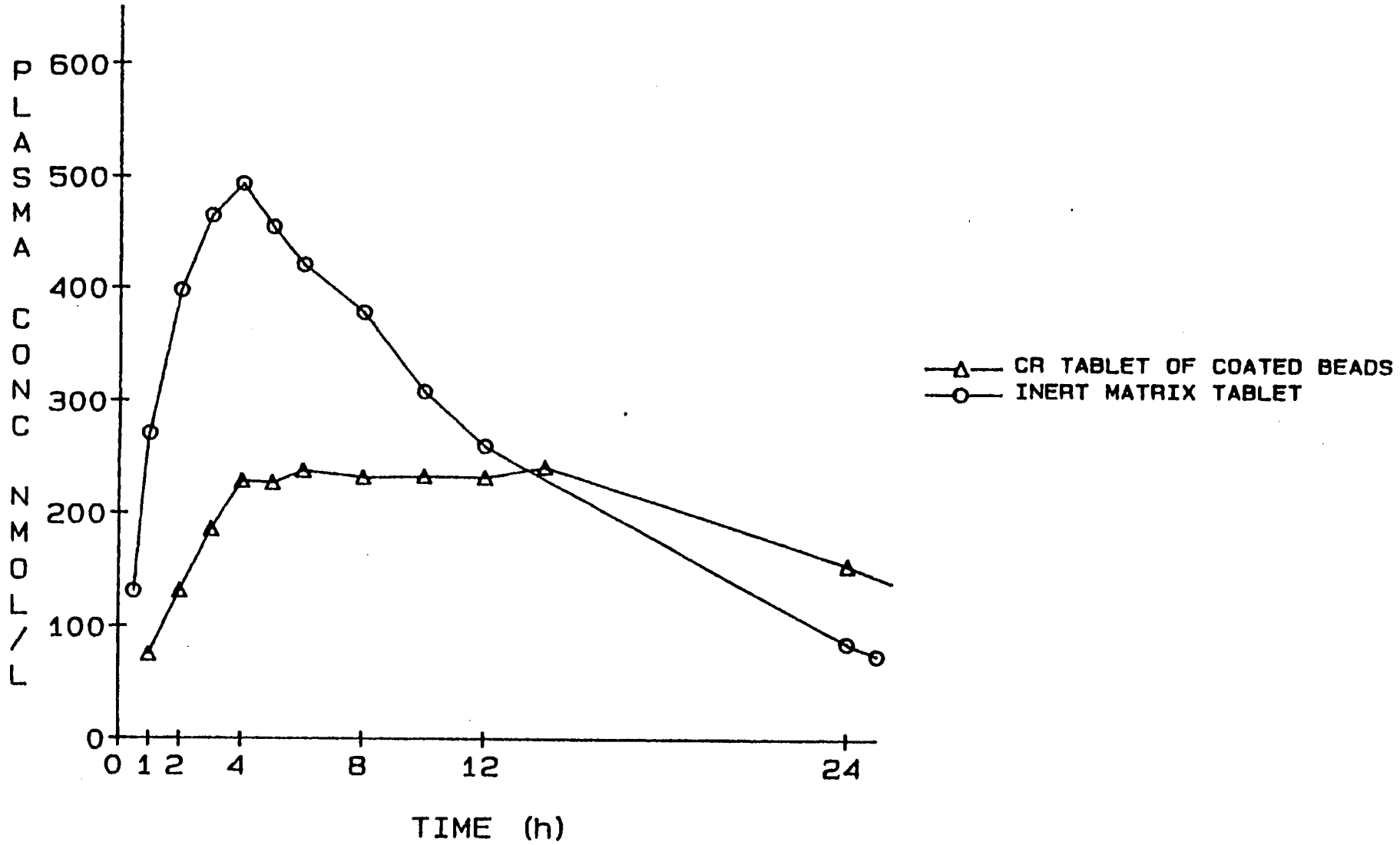

CUM. RELEASE %
0
20
40
60
80
100
0
4
8
12
16
20
24
TIME (h)
KCl-core 0.1-0.2 mm

FIG 2

FIGURE 3 . MEAN (n=10) PLASMA CONCENTRATIONS OF METOPROLOL AFTER SINGLE-DOSE ADMINISTRATION. DOSE: METOPROLOL CORRESP. 200 MG TARTRATE SALT



INTERNATIONAL SEARCH REPORT

PCT/SE86/00400

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 9/22

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A 61 K 9/00, /22, /24, /36, /52, /62
US Cl	424:16, 19, 23, 24, 35

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A, 0 013 263 (AB HÄSSLE) 9 July 1980 See claims 1-3, page 4, lines 21-30, page 5, line 21-page 6. line 10. page 7, lines 9-12. & BE, 880796 LU, 82025 AU, 53962/79 JP, 55087717 US, 4261971 CA, 1133394 SE, 426548 SE, 7813245 AT, 4371 AU, 531279 CH, 641358	1, 2, 3, 6, 7, 8, 11
Y	EP, A, 0 061 217 (PHARMATEC S.P.A.) 29 September 1982 See claims 1 and 3. .../...	1, 2, 3, 6, 7

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1986-12-03	1986 -12- 16
International Searching Authority	**Signature of Authorized Officer**
Swedish Patent Office	Agneta Tannerfeldt

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 12, because they relate to subject matter not required to be searched by this Authority, namely:

Method for the treatment of the human or animal body.

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	DE, A, 2 030 501 (BEIERSDORF AG) 30 December 1971 See claim 1, page 5, lines 1-9, page 7 lines 4-17, examples 1 and 3.	1, 4, 6, 7
A	GB, A, 1 542 414 (STANDARD TELEPHONES AND CABLES LIMITED) 21 March 1979	1, 5